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10/542,161	07/14/2005	Kaoru Miyamoto	033723-011	3998

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,161	MIYAMOTO ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *3-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/14/2005; 7/14/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appedix I; Appendix II*.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 7/14/2005, in which claims 1, 6 and 7 were amended. Receipt is also acknowledged of an amendment, filed 4/10/2008, in which claim 1 was amended. Currently, claims 1-7 are pending.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 4/10/2008 is acknowledged.

Claims 3-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/10/2008.

An examination on the merits of claims 1-2 follows.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt of the certified copy of the foreign priority document, JP 2003318343, is acknowledged. These papers have been placed of record in the file.

Information Disclosure Statement

Receipt of information disclosure statements, filed on 7/14/2005 and 7/14/2006, is acknowledged. The signed and initialed PTO 1449s have been mailed with this action.

The information disclosure statement filed 7/14/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered, except for the Mizutani reference. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

The abstract of the disclosure is objected to because it is not a single paragraph. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a protein (a) comprising "an amino acid sequence" of SEQ ID NO: 1, or (b) a protein having a transcriptional activator activity of SEQ ID NO: 1 and comprising "an amino acid sequence," where one or several amino acids are deleted, substituted or added in the amino acid sequence of (a). The phrase "an amino acid sequence of SEQ ID NO: 1" reads on a protein that contains any two or more contiguous amino acids of the sequence of SEQ ID NO: 1. The number of modifications that can be made to a protein comprising as few as two contiguous amino acids of SEQ ID NO: 1 results in proteins that may not have any sequence in common with the amino acid sequence of SEQ ID NO: 1. Thus, the claims read on virtually any amino acid sequence that must function as a transcriptional activator.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes the amino acid sequence of SEQ ID NO: 1. When this sequence is fused to a GAL4 DNA-binding domain, it functions to activate transcription (e.g., page2, lines 15-25; page 5, lines 1-5 and 28-32). The specification teaches that amino acids 25-63 of SEQ ID NO: 1 are essential for transcriptional activation activity (e.g., page 13, lines 28-30). Furthermore, the specification teaches that this region contains no typical transcriptional activation motifs (e.g., page 13, lines 28-30). No description is provided of

modifications of the region of amino acids 25-63 of SEQ ID NO: 1, which retain transcriptional activation activity.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of sequences comprising amino acids 25-63 of SEQ ID NO: 1. The results are not necessarily predictive of variants of this region which retain transcriptional activation activity. Thus, it is impossible for one to extrapolate from the sequence of amino acids 25-63 of SEQ ID NO: 1 those amino acid substitutions, deletions or additions of this sequence that would necessarily meet the functional characteristics of the rejected claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of transcriptional activator proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

"A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). In the instant case, one cannot envision the operability of species other than proteins comprising amino acids 25-63 of SEQ ID NO: 1. The specification teaches that this region contains no known typical transcriptional activation motifs, and one could not rely upon a known structure-function relationship to predict the operability of sequence variants of this region of SEQ ID NO: 1 or variants lacking the sequence of amino acids 25-63 of SEQ ID NO: 1.

Given the very large genus of transcriptional activator proteins encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the structure than can be varied within amino acids 25-63 of SEQ ID NO: 1, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those modifications within amino acids 25-63 of SEQ ID NO: 1 that satisfy the functional limitations of the claims with regard to transcriptional activation activity.

Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 1 and 2.

Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Claim 2 is drawn to a medical agent for the activation of transcription. The structure of the medical agent is defined as a protein (a) comprising "an amino acid sequence" of SEQ ID NO: 1, or (b) a protein having a transcriptional activator activity of SEQ ID NO: 1 and comprising "an amino acid sequence," where one or several amino acids are deleted, substituted or added in the amino acid sequence of (a). The phrase "an amino acid sequence of SEQ ID NO: 1" reads on a protein that contains any two or more contiguous amino acids of the sequence of SEQ ID NO: 1. The number of modifications that can be made to a protein comprising as few as two contiguous amino acids of SEQ ID NO: 1 results in proteins that may not have any sequence in common with the amino acid sequence of SEQ ID NO: 1. Thus, the claims read on virtually any amino acid sequence that must function as a

transcriptional activator. The nature of the invention is complex in that the transcriptional activation must result in a therapeutic effect.

Breadth of the claims: The claims are broadly drawn to the use of virtually any amino acid sequence as a transcriptional activator as a medical agent. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

Guidance of the specification and existence of working examples: The specification envisions the use of the claimed medical agent for the treatment of diseases such as sterility disease, polycystic ovary syndrome, endometriosis, precocious puberty, osteoporosis, and other diseases related to abnormalities of the reproductive organs (e.g., page 7, lines 16-25).

The specification teaches the isolation of a cDNA sequence encoding an HMG-box domain from a cDNA library of rat ovarian granulosa cells (e.g., page 2, lines 15-18; Example 1). The full-length cDNA sequence is provided in SEQ ID NO: 2 and encodes the protein of SEQ ID NO: 1. The protein is named GCX-1 (granulosa cell HMG-box protein-1) (e.g., page 2, lines 15-19). The specification teaches the following functions for the protein: (1) interaction with GIOT-1 (gonadotropin-inducible ovarian transcription factor-1); and (2) transcriptional activation when fused to a DNA binding domain such as GAL4 (e.g., Examples). The specification teaches that GCX-1 has a single HMG-box motif similar to specific type HMG box proteins (proteins that recognize a specific DNA sequence on their target gene), but has no sequence similarity to these proteins (e.g., paragraph bridging pages 5-6). However, the HMG box of GCX-1 has sequence similarity to the nonspecific type HMG-box, which is usually present in two or more copies of the protein and interacts with DNA in a non-specific manner (e.g., paragraph bridging pages 5-6). Further, the specification teaches that the target genes of

GCX-1 are unknown (e.g., page 13. lines 5-8). Accordingly, the genes regulated by GCX-1 cannot be related to a specific disease.

The specification teaches the gene expression pattern of GCX-1 in rats. GCX-1 is expressed in hypothalamus, pituitary, testis, uterus and ovary (e.g., page 10, lines 27-28). Based upon this expression pattern, the specification concludes that GCX-1 may function on the hypothalamo-pituitary-gonadal axis; however a specific function for GCX-1 in the hypothalamo-pituitary-gonadal axis is not provided.

There are no working examples in which a protein comprising a sequence of SEQ ID NO: 1 or variant thereof is used as a medical agent to induce a therapeutic effect for any disease in any disease model.

Predictability and state of the art: As discussed above, the target genes for GCX-1 are not known, and the specific role of GCX-1 in the hypothalamo-pituitary-gonadal axis is not provided. Thus, it would be unpredictable to treat a disease by activating the expression of unknown genes with unpredictable effects. There is no prior art of record that teaches a relationship between the function of GCX-1 protein and disease related to the hypothalamo-pituitary-gonadal axis or abnormalities of the reproductive organs such that one could predict the effect of the protein on the disease symptoms.

The prior art teaches that GCX-1-interacting protein GIOT-1 is a transcriptional repressor expressed in the pituitary, adrenal, testis and ovary (Mizutani et al. Molecular Endocrinology, Vol. 15, No. 10, pages 1693-1705, 2001, cited on the IDS filed 7/14/2005; e.g., page 1694, left column, 1st full paragraph). Given the transcriptional repression activity of GIOT-1 and the transcriptional activation activity of GCX-1, the functional consequences of the interaction of

these two proteins in the pituitary, testis or ovary are unclear. There is no art of record that teaches the functional consequences of GCX-1 and GIOT-1 interaction.

The nature of the claimed invention is unpredictable, because the claims encompass many sequence variants that may not retain the ability to modulate the transcription of the same genes. For example, Wilkinson et al (Nature Immunology, Vol. 3, No. 3, pages 272-280, Epub February 19, 2002) teach a protein encompassed by the claims, which is involved in the regulation of T-cell development rather than the hypothalamo-pituitary-gonadal axis or reproductive organs. The wide range of sequences encompassed by the claims renders the invention highly unpredictable with regard to the target organs and target genes for the encompassed transcriptional activator proteins. Thus, one would not know how to use these proteins as a medical agent to achieve a therapeutic effect.

Amount of experimentation necessary: Given the lack of guidance in the specification and prior art, the quantity of experimentation to make and use the claimed proteins as medical agents is extremely large. First, one would have to choose a protein falling with the scope of the claims. Next one would be required to perform a large amount of trial and error experimentation to find a disease that is treatable with the protein. This would require the screening a large number of disease model systems, which are not limited by a target organ, target genes, or specific phenotype to be treated. The ability to activate transcription does not provide sufficient guidance to identify treatable diseases, and thus a large amount of experimentation is required to provide a nexus between the protein sequence and transcriptional activation function and a therapeutic effect for a specific disease.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claim 2 is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Zappavigna et al (The EMBO Journal, Vol. 15, No. 18, pages 4981-4991, 1996, cited in a prior action; see the entire reference).

The claims are drawn to a protein (a) comprising "an amino acid sequence" of SEQ ID NO: 1, or (b) a protein having a transcriptional activator activity of SEQ ID NO: 1 and comprising "an amino acid sequence," where one or several amino acids are deleted, substituted or added in the amino acid sequence of (a). The phrase "an amino acid sequence of SEQ ID NO: 1" reads on a protein that contains any two or more contiguous amino acids of the sequence of SEQ ID NO: 1. The number of modifications that can be made to a protein comprising as few as two contiguous amino acids of SEQ ID NO: 1 results in proteins that may not have any sequence

in common with the amino acid sequence of SEQ ID NO: 1. Thus, the claims read on virtually any amino acid sequence.

Zappavigna et al teach transcriptional activator proteins, including HMG1 and HOX proteins (e.g., Abstract; pages 4983-4984, HMG1 enhances HOXD9-mediated transcriptional activation; Figures 1 and 4).

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Wilkinson et al (Nature Immunology, Vol. 3, No. 3, pages 272-280, Epub February 19, 2002; see the entire reference).

The claims are drawn to a protein (a) comprising "an amino acid sequence" of SEQ ID NO: 1, or (b) a protein having a transcriptional activator activity of SEQ ID NO: 1 and comprising "an amino acid sequence," where one or several amino acids are deleted, substituted or added in the amino acid sequence of (a). The phrase "an amino acid sequence of SEQ ID NO: 1" reads on a protein that contains any two or more contiguous amino acids of the sequence of SEQ ID NO: 1. The number of modifications that can be made to a protein comprising as few as two contiguous amino acids of SEQ ID NO: 1 results in proteins that may not have any sequence in common with the amino acid sequence of SEQ ID NO: 1. Thus, the claims read on virtually any amino acid sequence.

Wilkinson et al teach the mouse TOX protein (thymus HMG box) (e.g., page 273, left column; Web Figure 1). The mouse TOX protein comprises an amino acid sequence of SEQ ID NO: 1 (see the attached alignment in Appendix I).

Claims 1 and 2 are rejected under 35 U.S.C. 102(e) as being anticipated by Isogai et al (US Patent No. 6,979,557 B2; see the entire reference).

The claims are drawn to a protein (a) comprising "an amino acid sequence" of SEQ ID NO: 1, or (b) a protein having a transcriptional activator activity of SEQ ID NO: 1 and comprising "an amino acid sequence," where one or several amino acids are deleted, substituted or added in the amino acid sequence of (a). The phrase "an amino acid sequence of SEQ ID NO: 1" reads on a protein that contains any two or more contiguous amino acids of the sequence of SEQ ID NO: 1. The number of modifications that can be made to a protein comprising as few as two contiguous amino acids of SEQ ID NO: 1 results in proteins that may not have any sequence in common with the amino acid sequence of SEQ ID NO: 1. Thus, the claims read on virtually any amino acid sequence.

Isogai et al teach the protein of SEQ ID NO: 1886 (e.g., column 2; Table 1 at column 9). The protein of Isogai et al comprises an amino acid sequence of SEQ ID NO: 1 (see the attached alignment in Appendix II).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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